Relationships of Lead in Breast Milk to Lead in Blood, Urine, and Diet of the Infant and Mother

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We have obtained stable lead isotope and lead concentration data from a longitudinal study of mobilization of lead from the maternal skeleton during pregnancy and lactation and in which the newly born infants were monitored for 6 months postpartum to evaluate the effects of the local environment on lead body burden of the infant. Samples of maternal and infant blood, urine, and diet and especially breast milk were measured for 21 mothers and 24 infants. Blood lead concentrations were less than 5 μg/dl in all except one subject. The mean lead concentration in breast milk ± standard deviation was 0.73 ± 0.70 μg/kg. In seven subjects for whom serial breast milk sampling was possible, the lead concentration varied by factors of from 2 to 4, and for three subjects there was an increase at or after 90 days postpartum. For the first 60–90 days postpartum, the contribution from breast milk to blood lead in the infants varied from 36 to 80%. Multiple linear regression analyses indicated statistically significant relationships for some of the variables of isotope ratios and lead concentrations between breast milk, blood, urine, and diet for infants and mothers. For example, the analyses revealed that both a mother's breast milk $^{207}Pb/^{206}Pb$ and $^{206}Pb/^{204}Pb$ ratios and lead concentration provide information to predict her infant's blood $^{207}Pb/^{206}Pb$ and $^{206}Pb/^{204}Pb$ ratios. The major sources of lead in breast milk are from the maternal bone and diet. An evaluation of breast milk lead concentrations published over the last 15 years indicates that studies in which the ratio of lead concentrations in breast milk to lead concentrations in whole maternal blood (×100) were greater than 15 should be viewed with caution because of potential contamination during sampling and/or laboratory analyses. Selected studies also appear to show a linear relationship between breast milk and maternal whole blood, with the percentage of lead in breast milk compared with whole blood of <3% in subjects with blood lead levels ranging from 2 to 34 μg/dl. The levels of lead in breast milk are thus similar to those in plasma. Breast-fed infants are only at risk if the mother is exposed to high concentrations of contaminants either from endogenous sources such as the skeleton or exogenous sources. *Key words*: blood, breast milk, infant, intake, isotopes, lead, mother, urine. *Environ Health Perspect* 106:667–674 (1998). [Online 3 September 1998]
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Owing to its unique nutritional and immunological characteristics, human milk is the most important food source for infants. Breast milk can, however, also be a pathway of maternal excretion of toxic elements such as lead, and these toxins impact most severely on the newborn at a time of rapid development of the central nervous system (*1*). Apart from contributions from maternal sources during pregnancy such as from the skeleton (*2,3*), other potential lead sources for the infant are mainly dietary, that is, from breast milk, infant formula, and baby foods.

Data for rodents has shown that lead mobilized from the skeleton is transferred to the suckling during lactation (*4,5*) and that lactational transfer after current or recent exposure to lead in dams was considerably higher than placental transfer (*6*).

In humans, Gulson et al. (*3*) showed that there was an increased and sustained mobilization of maternal skeletal lead during lactation compared with during pregnancy; thus, the following question arises: Are the infants at more risk from breast-feeding than from formula feeding? Several studies have observed relatively high concentrations of lead in breast milk that pose a potential hazard to the infant. Uptake of lead from the diet in young infants is poorly understood and relies almost solely on the limited data of Alexander et al. (*7*), Ziegler et al. (*8*), and Ryu et al. (*9,10*) obtained during the 1970s and 1980s when environmental lead was higher and control of laboratory contamination was less complete.

Not only are the relationships between uptake of lead from breast milk and formula extremely important, but as the ultimate source of the lead is from the mother, it is also critical to understand more about the relationships between breast milk and the maternal system.

We have obtained data from a longitudinal study of mobilization of lead from the maternal skeleton during pregnancy and lactation, and in which the newly born infants were monitored for 6 months postpartum to evaluate the effects of the local environment on lead body burden of the infant. From changes in the isotopic composition of blood and urine compared with those from dietary intake and other sources, it is possible to provide answers to the questions: 1) What is the contribution of lead in breast milk and infant diet to blood lead and excretion of lead? and 2) What is the relationship of lead in breast milk to lead in maternal blood, urine, and diet?

Methods

Subjects

Fifteen adult females have been monitored during gestation and for up to 6 months or longer after pregnancy to determine the effects of lactation on mobilization of lead from skeletal stores. Participants were female immigrants to Australia who were of childbearing age (18–35 years) and whose skeletal lead isotopic composition was determined to be different from that in their current environment. Data for the pregnant immigrants were matched with second-generation Australian pregnant women who served as the control group. Signed consent forms were obtained from each volunteer. This consent form had been reviewed and approved by the Ethics Committee of St. Vincent's Hospital of Sydney, the University of Adelaide in Australia, and the U.S. National Institutes of Health. As part of the entry requirements into Australia, all subjects were declared medically fit. Details of the maternal sampling and results of their blood,

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urine, and dietary intake have been published in several papers (*2,3,11*).

Sixteen infants (migrant infants) were born to 15 migrant mothers, and their data were compared with 8 infants (Australian infants) who were born to 6 multigenerational Australian controls.

Sampling

Venous blood samples were collected wherever possible at 60, 120, and 180 days postpartum following a rigorous protocol described in Gulson et al. (*11*). Because of the operational and social difficulties associated with collecting the required number of venous blood samples from all the newborn infants, urine samples were also collected at 10, 30, 60, 90, 120, 150, and 180 days into pediatric urine collectors and transferred into precleaned polyethylene bottles. Angle et al. (*12*) and Gulson et al. (*13*) have shown that the isotopic compositions of urine generally conform well with those for blood with correlations of better than 0.9.

Breast milk was collected monthly and expressed directly into precleaned polyethylene bottles. For one subject (1043), two early samples were collected using a breast pump; although we were concerned that these samples may have been contaminated, breast pump collection is a routine method used by Swedish investigators, with no apparent contamination (*14,15*).

Infant formula was collected monthly. In some cases, different brands were used and these were collected separately. Mothers were requested to prepare the formula with boiled water from a fully flushed faucet, and the boiled water was also collected. When intake of solid food began, a composited meal was prepared by the mother and dispensed into precleaned polyethylene containers.

Fully flushed drinking water was collected from the kitchen faucet after an additional 30-sec flush. House dust was collected as dust fall accumulation using petri dishes placed in at least two locations in the residence for 3-month collections as part of the monitoring of the mother (*16*).

Analytical Methods

All sample preparation was performed in purpose-built low contamination laboratories (clean rooms) incorporating features such as filtered air intake and laminar flow hoods.

Blood. To minimize sample heterogeneity, the total blood sample was predigested in ultrapure concentrated nitric acid and an aliquot of <1 g was removed to a clean teflon vessel. A ^{202}Pb spike solution of known isotopic composition and lead concentration was added to the aliquot to obtain the concentration of lead and isotopic composition of the unknown sample in the one analysis (the isotope dilution method). [^{202}Pb is not naturally occurring and is produced in cyclotrons as a by-product of preparation of thallium used in treatment of thyroid abnormalities.] Lead was separated from interfering elements such as Fe and Zn by anion-exchange chromatography in a hydrobromic acid medium.

Urine. An aliquot of 5–10 ml urine was spiked with ^{202}Pb and digested in ultrapure nitric acid, and lead separation followed that for blood samples.

Food, formula, and breast milk. After the sample was "spiked" with ^{202}Pb and predigested in ultrapure nitric acid, the sample was digested in a laboratory microwave oven. Because of the low concentrations of lead, especially in breast milk (usually less than 1 ppb Pb), large samples up to 20 g were required for analysis to enable high quality isotopic data to be obtained and minimize chances of contamination during processing. Lead was then separated as for blood samples.

Isotope ratio measurement. Fractions of the purified lead samples were loaded onto a rhenium filament using the silica gel technique and analyzed for lead isotope composition on a thermal ionization mass spectrometer or TIMS (VG-ISOMASS 54E; VG Isotopes, Winsford, UK) run in fully automatic mode. Isotopic ratios were measured as $^{208}Pb/^{206}Pb$, $^{207}Pb/^{206}Pb$, and $^{206}Pb/^{204}Pb$. Precision estimates on the isotopic ratios have been defined by a repetition of the digestion/lead separation/mass spectrometry stages of the same samples of blood, urine, and water; this was required for validation of the Biokinetics of Lead in Human Pregnancy project. The precisions we allocated our data were ± 0.2% (2 σ) on the $^{206}Pb/^{204}Pb$ ratio and ± 0.1% on the $^{208}Pb/^{206}Pb$ and $^{207}Pb/^{206}Pb$ ratios. Data were normalized to the accepted values of the international standard (National Institute of Standards and Technology, Gaithersburg, MD) Standard Reference Material 981 by applying a correction factor of + 0.08% atomic mass units to allow comparisons between laboratories. A measurement of the environmental lead acquired by the sample throughout the entire preparation analysis procedure was obtained in the form of a lead blank measurement. The amount of contamination detected in blanks was generally around 200 pg for blood and urine and less than 300 pg for food and breast milk. As the blanks contributed negligibly to the lead in the sample in all except breast milk, no blank corrections to the data were performed.

Data Analysis

Multiple linear regression analyses were performed using Stata Release 4 (Stata Corporation, College Station, TX) with a stepwise forward selection to explore the relationships for the variable isotope ratios ($^{207}Pb/^{206}Pb$, $^{206}Pb/^{204}Pb$) and lead concentrations between breast milk, blood, urine, and diet in the infants and mothers. Descriptive statistics and *t*-tests were performed using SPSS version 7.5 (SPSS, Chicago, IL).

For pharmacokinetic modeling, we used the U.S. EPA Integrated Uptake Exposure Biokinetic Model, version 0.99d (*17*) and the physiologically-based pharmacokinetic model of O'Flaherty (*18*) and O'Flaherty and Reponen (*19*).

Justification of (Small) Number of Subjects

Papers such as this one are commonly criticized by some researchers as having a small number of subjects, which do not readily lend themselves to statistical manipulation. This criticism may be due to a lack of understanding of isotope studies, to which the concept of analysis numbers does not translate to one result for each sample. This misunderstanding is common because the use of the lead isotope technique in health and environmental research has only really come to be used over the past decade, and it is a highly specialized field.

As mentioned above, the lead isotope technique by thermal ionization mass spectrometry is a high precision technique that provides three independent measurements (isotopic ratios $^{208}Pb/^{206}Pb$, $^{207}Pb/^{206}Pb$, and $^{206}Pb/^{204}Pb$) for each sample, in addition to measuring lead concentration. For the $^{207}Pb/^{206}Pb$ ratio, numbers in the fourth decimal place can be significant.

Thus, the high precision measurements of isotopic ratios allow for a high discriminatory power with minimal statistical manipulation, and it is possible to provide definitive answers from a small number of samples. This compensates for the drawbacks of the method (lead isotopic measurements are costly because they are extremely labor intensive and require expensive equipment and ultraclean laboratories). Low sample numbers are also advantageous for participants in the study because sampling methods involve some degree of personal invasion.

The use of migrants and Australians for the study adds an additional precision control. We have found (through the biokinetics study) that the lead in the blood of Australian subjects has an isotopic fingerprint or signature clearly distinct from that found in subjects from many other countries. The isotopic ratios of the two groups differ by a factor 29 times greater than our precision limits. These differences arise

because the lead in the Australian environment is derived mainly from mineral deposits that are geologically ancient, whereas the lead in most other countries is derived from geologically young mineral deposits. Blood $^{206}Pb/^{204}Pb$ ranges from 18.0 to 18.5 in migrants and 17.0 or less in Australians (*2,3,11*). This is a minimum difference of 6%.

Results

Blood lead concentrations in 14 of the 15 adult immigrant subjects and for all Australian controls were less than 5 µg/dl. Cord blood lead concentrations in the migrants ranged from 0.91 to 3.61 µg/dl (geometric mean 2.02 µg/dl) and in the Australian controls from 0.96 to 3.67 µg/dl (geometric mean 2.51 µg/dl).

The duration of breast-feeding varied considerably (Table 1); infants were breast-fed for over 6 months (subjects 2016, 2043, 2065, 2066, 2085, 2093), less than 1 week, or not at all (subjects 3009, 2055, 2069, 2090, 3057). The mean lead concentration in breast milk ± standard deviation (SD) was 0.73 ± 0.70 µg/kg, with a range from 0.09 to 3.1 µg/kg (n = 48). There was no statistical difference in milk lead concentration between the migrant and Australian infants ($p \leq 0.4$, two-tailed t-test).

Serial sampling of breast milk was possible in seven cases (migrant subjects 1016, 1022, 1041, 1042, 1043, 1056 and Australian subject 1065), and the analytical data for additional cases are yet to be obtained (1066, 1085, 1093). For the seven cases for which data are available, there were changes in lead concentration by factors of 2–4 (Table 2, Fig. 1). In three of the six cases of migrant subjects (1022, 1041, 1056), there were variable increases in lead concentration at, or after, about 90 days postpartum, but there appeared to be no systematic trends in the overall variation. In most cases, the breast milk exhibited decreases in $^{206}Pb/^{204}Pb$ over time (Fig. 2).

Lead concentrations in formula were generally low, with a geometric mean of 1.8 µg Pb/kg (median 1.9) and a range of 0.36–4.3 µg Pb/kg (n = 53). In contrast, the isotopic composition of the formula exhibited a large range depending on the country of origin of the ingredients. The $^{206}Pb/^{204}Pb$ ranged from 16.0 to 19.2, which is over 100 times our experimental error. For example, soy products for the lactose-intolerant Australian infants (2049 and 3049) ranged from 16.7 to 19.2. The low value reflects ingredients sourced mainly from Australia and the higher value ingredients from the United States, the latter confirmed by the manufacturer.

Lead concentrations in the baby food (beikost) were up to three times that found in the formula, with a geometric mean of 4.1 µg Pb/kg (median 3.5) and a range of 1.4–27 µg Pb/kg. The differences between formula and baby food were statistically significant ($p \leq 0.003$, two-tailed t-test).

Fully flushed drinking water and boiled water used for making up formula had low concentrations of lead, generally <3 µg Pb/l, and the isotopic ratios were less than 17 in all these residences (*20*).

Results of the multiple linear regression analyses are shown in Table 3. In the analysis of infant's urine and mother's breast milk, the urine outcome variable to be predicted, e.g., urine $^{207}Pb/^{206}Pb$, was regressed on the available breast milk variables, e.g., milk $^{207}Pb/^{206}Pb$, $^{206}Pb/^{204}Pb$, and lead concentration. Analysis was performed on the most complete data sets at 60 ± 5 days and for subjects 2022, 2041, 2042, 2043, 2056, and 2096.

Table 1. Subjects and dietary information

Identifier	Breast-fed (days)	Start of formula (days)	Start of food (days)
Migrant infants			
2009	14	15	100
3009	0	1	80
2016[a]	>180	–	120
2022	150	75[b]	180
2035[a]	>180	120[b]	180
2041	120	120[b]	120
2042	60	61	150
2043	>180	–	150
2045	60	61[b]	120
2052	60	61	90
2055[a]	0	1[c]	>180[d]
2056	165	166	120
2069	0	1	90
2090	0	1	150
2096[a]	150	151	140
2097	85	86	165
Australian infants			
2049	14	15[c]	130
3049[a]	30	1[b,c]	120
2057	15	16	90
3057[a]	0	1[c]	90
2065	>180	–	120
2066[a]	>180	–	170
2085[a]	>180	–	180
2093	>180	–	120

[a]Full blood sampling regime not possible.
[b]Formula was a supplement to breast milk.
[c]Changed formula.
[d]Was not fed solids but was given up to 250 ml/day camomille tea from birth.

Table 2. Variations in lead concentration in breast milk for serially sampled subjects

Identifier	Mean ± SD (µg/kg)	Range	n
1016	0.15 ± 0.04	0.09–0.21	7
1022	0.57 ± 0.39	0.27–1.24	6
1041	0.32 ± 0.13	0.20–0.50	4
1042	0.33 ± 0.06	0.28–0.40	3
1043	0.81 ± 0.26	0.57–1.3	6
1056	1.36 ± 0.72	0.64–2.09	5
1065	0.32 ± 0.17	0.18–0.62	5

SD, standard deviation.

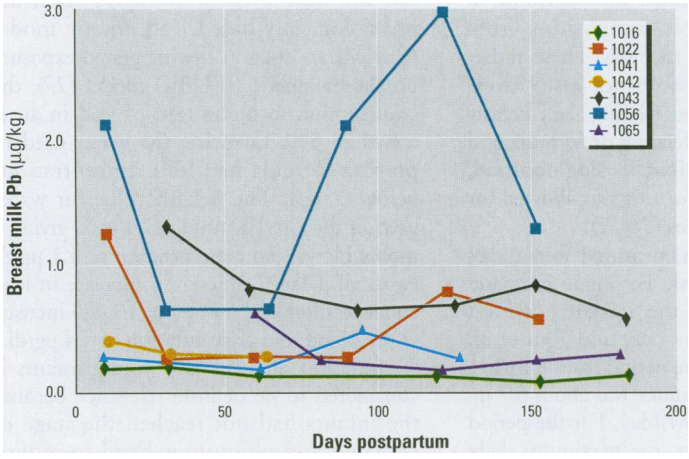

Figure 1. Lead concentration in breast milk over time for subjects from whom it was possible to obtain serial samples. A sample for subject 1016 at 352 days is not shown, but has similar low lead concentration (0.11 µg/kg) as the earlier samples.

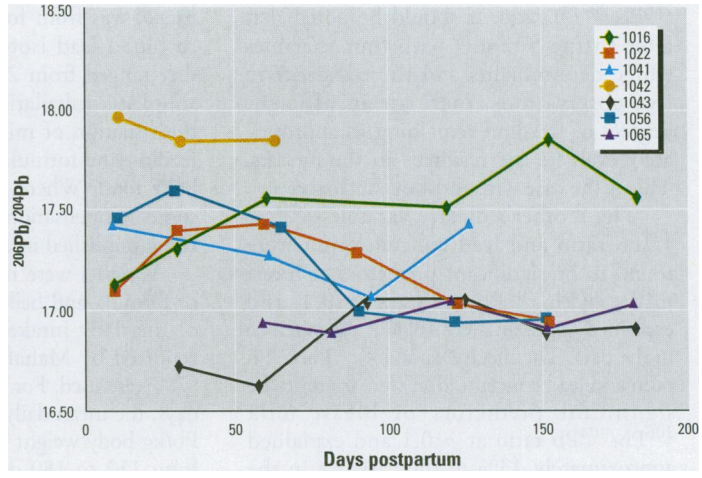

Figure 2. Lead isotope ratio $^{206}Pb/^{204}Pb$ in breast milk over time for subjects from whom it was possible to obtain serial samples. A sample for subject 1016 at 352 days is not shown, but has similar isotopic compositions to the earlier samples.

Table 3. Results from multiple linear regression analyses

Sample type	Dependent variable	Independent variable	Coefficient	*p*-Value	90% Confidence interval
Infants					
M vs. B	B $^{207}Pb/^{206}Pb$	$^{207}Pb/^{206}Pb$	0.5288	0.081	0.061–0.997
		Pb conc	-0.0395	0.086	-0.076–0.003
	B $^{206}Pb/^{204}Pb$	$^{207}Pb/^{206}Pb$	-12.0964	0.108	-24.74–0.556
		Pb conc	0.86246	0.124	-0.116–1.184
F vs. B	BPb conc	$^{206}Pb/^{204}Pb$	-349.9	0.047	692–7.533
		$^{207}Pb/^{206}Pb$	-15.5734	0.050	-31.188–0.0411
		Pb conc	0.2706	0.055	-0.00998–0.5513
F vs. U	U$^{207}Pb/^{206}Pb$	Pb conc	0.00557	0.016	-0.00967–0.00148[a]
	U$^{206}Pb/^{204}Pb$	Pb conc	0.1379	0.015	0.03846–0.23744[a]
	UPb conc	$^{207}Pb/^{206}Pb$	19.888	0.003	12.7818–26.995[a]
		Pb conc	-0.18093	0.003	-0.2490–0.11287[a]
		Time	0.68321	0.003	0.4458–0.9206[a]
Mothers					
M vs. F	M$^{207}Pb/^{206}Pb$	$^{207}Pb/^{206}Pb$	-0.04739	0.060	-0.08604–0.008642
		Pb conc	0.005316	0.060	0.009596–0.009672
	M$^{206}Pb/^{204}Pb$	$^{206}Pb/^{204}Pb$	1.02837	0.069	0.141969–1.91476
		Pb conc	0.112462	0.074	-0.21227–-0.012677

Abbreviations: M, breast milk; B, blood; F, formula or food; U, urine; conc, concentration.
[a]95% confidence intervals.

These stepwise regressions did not yield any useful information. Individual variables, and the best two (out of three) were also regressed on the three urine variables, but not even marginally significant associations were found.

The mother's $^{207}Pb/^{206}Pb$ ratio and lead concentration in breast milk were found to be statistically significant predictors of an infant's blood lead $^{207}Pb/^{206}Pb$ ratio at $p<0.1$. Taken together, these two breast milk variables explain more than 72% of the variance in an infant's blood lead $^{207}Pb/^{206}Pb$ ratio. The mother's breast milk $^{207}Pb/^{206}Pb$ ratio was found to be a marginally significant predictor of an infant's blood $^{206}Pb/^{204}Pb$ ratio at $p<0.1$; however, breast milk lead concentration was not found to be statistically significant at this level. Taken together, these two breast milk variables explain more than 62% of the variance in an infant blood $^{206}Pb/^{204}Pb$ ratio. It should be noted that after fitting a model with four variables (three determinants and the constant) to five observations, there are insufficient degrees of freedom remaining to appropriately evaluate the residuals to the models. This is the case with most of the analyses.

The mother's dietary variables $^{206}Pb/^{204}Pb$ ratio and lead concentration were found to be significant predictors of breast milk $^{207}Pb/^{206}Pb$ ratio at $p<0.1$ and explained approximately 48% of the variance in the data. The dietary variables $^{206}Pb/^{204}Pb$ ratio and lead concentration were found to be significant predictors of breast milk $^{206}Pb/^{204}Pb$ ratio at $p<0.1$ and explained approximately 43% of the variance in the data. The dietary variables $^{207}Pb/^{206}Pb$ and $^{206}Pb/^{204}Pb$ ratios and lead concentration were found to be highly correlated with the outcome variable and with each other. Consequently, three linear regression models were fitted, each explaining between 67% and 74% of variation in the outcome variable. Each predictor of breast milk lead concentration was significant at $p<0.05$.

Assuming that other sources of lead contribute minimally to blood lead concentration, as discussed below, it is possible to estimate the contribution to blood lead concentration in infants from breast milk and/or formula/food using two-component mixing relationships (*21*). With the infants' blood as one component and breast milk or formula as the other, the amounts of lead from dietary intake are shown in Table 4. For migrant infants the component of lead in blood at 60 or 90 days from breast milk (plus formula in the case of subject 2022) varied from 36 to 80%. For migrant and Australian infants whose main dietary intake was from formula, the contribution to blood lead isotopic composition from diet ranged from 24 to 68%. These rather simplistic calculations do not easily cover the situation of mixed feeding, i.e., breastfeeding and formula feeding or formula and baby food. Where mixed feeding occurred, some compensation for this was allowed for using published intakes (*10,22*).

Weights were not measured for intakes of formula and beikost. To obtain estimates of the daily intakes, the amounts of food reported by Mahaffey (*22*) and Ryu et al. (*10*) were used. For the period from 8 to 111 days, the mean daily intake was about 0.7 µg Pb/kg body weight (bw)/day. For the period from 112 to 180 days, the maximum daily intake for subject 2057, whose food concentrations were high at 15 and 7.7 µg Pb/kg, ranged from 0.6 to 1.5 µg Pb/kg bw/day.

Table 4. Contribution of lead from breast milk or formula to lead in whole blood of infants

Identifier	% Contribution in blood from breast milk or formula	Interval (days)
Migrant infants[a]		
2009	68[b]	0–90
3009	44[b]	0–63
2022	80[b,c]	0–91
2041	64[c]	0–62
2042	24[b]	63–131
2043	39[c]	0–58
2056	36[c]	0–66
Australian controls		
2049	30[b]	0–124
2057	34[b]	0–90

[a]Blood samples were unavailable for infant 2016.
[b]Contribution of lead from formula.
[c]Contribution of lead from breast milk.

Discussion

Sources of Lead and Dietary Intake

Figure 2 shows that the lead isotope ratios for breast milk of the six immigrant nursing mothers are consistent with a significant lead fraction from maternal bone lead releases to blood lead. This is to be expected from our previous finding that bone lead is a significant fraction of maternal blood lead during lactation (*3*). Furthermore, maternal blood via plasma is the vehicle for lead transport to breast milk. The suggestion of a significant contribution of bone lead is consistent with the statistical analyses which indicate that at least 30% of lead in breast milk can be accounted for by source(s) other that the maternal diet. Apart from the skeletally derived lead, dietary lead is the most important exposure contributing to body burden in these newborn infants. Lead in urban air, where most of the infants reside, is currently <0.1 µg Pb/m^3, has a $^{206}Pb/^{204}Pb$ ratio of <17, and is also considered to contribute negligibly to blood or urine (*11*). If the low soil and dust levels of 40 mg/kg from the physiologically based lead kinetic model (PBKM) are used in the integrated exposure uptake biokinetic (IEUBK) model (*17*), the contribution to blood lead of lead in air is less than 5%. Likewise, the water used to prepare formula had lead concentrations below 3 µg/l. The default value for water used in the IEUBK model is 4 µg/l, giving a model blood lead concentration of 4.1 µg/dl (with all default values). An increase in lead concentration in the water to 10 µg/l increases the blood lead concentration to 4.4 µg/dl.

Soil and dust in these young infants is considered to be of little relevance because the infants had not reached the stage of crawling and ubiquitous hand-to-mouth activity. Nevertheless, airborne dust in the residences, monitored for ongoing 3-month intervals for the maternal aspects of the study

using the petri-dish approach (*16*), has low lead loading and low $^{206}Pb/^{204}Pb$ ratios (*20*).

Low lead concentrations of 0.7 µg Pb/kg lead in breast milk would suggest that breast milk contributes minimally to blood lead concentration. Applying a range in breast milk lead concentrations from 2 to 4 µg Pb/kg in either the U.S. EPA IEUBK model (*17*) or the PBKM model of O'Flaherty (*18,19*) results in negligible change in blood lead concentration for an infant up to 1 year old. O'Flaherty does not distinguish between breast milk and formula in her PBKM model.

In contrast to the negligible changes shown by the modeling, the calculations outlined above indicate that for the period from birth to 60–90 days, 36–80% of lead in infant blood derives from breast milk (and/or formula). As mentioned above, the remaining 20–64% of lead does not derive from air, water, and dust. We argue in a companion paper that the extra lead not coming from breast milk and/or formula derives from the infant skeleton associated with high bone turnover (*23*).

We do not observe any difference in the amount of lead in blood from breast milk or formula, which is consistent with observations of Ryu et al. (*9*). This also suggests that mixed feeding for some infants does not impact significantly on blood lead concentration.

If formula is the main source of dietary intake in the first 3 months postpartum, then the mean daily intake is about 0.7 µg Pb/kg bw/day. Similar values were estimated for the 3–6-month period for most subjects, but in the case of subject 2057 whose first sampled blood lead concentration was 3.7 µg/dl, the dietary intake in one quarter was double the above amount (i.e., increased from 0.6 to 1.5 µg Pb/kg bw/day) because of the high concentrations of lead in the beikost.

Data for daily intake and fractional absorption of lead in very young infants, although widely quoted and used in pharmacokinetic models, are very sparse and were obtained in the days when dietary intakes were very much higher than current intakes. Thus, Alexander et al. (*7*) conducted 11 balance studies with eight subjects ranging in age from 3 months to 8 years; only one child was less than 6 months of age. Intakes averaged 10.6 µg Pb/kg bw/day (range 5–17 µg Pb/kg/day), with absorption averaging 53% of intake and retention averaging 18% of intake. In their investigation of 61 metabolic balance studies with 12 infants ranging in age from 14 to 746 days and whose lead intakes were greater than 5 µg Pb/kg/day, Ziegler et al. (*8*) reported an average absorption of 41.5% and net retention of 31.7% of intake. In the Ziegler et al. study, only one infant was studied from "birth" (14 days), two were studied from 72 and 83 days, and the rest were over 4 months old. Ziegler et al. (*8*) also reported that 7 of the 28 balance studies with lead intakes of <5 µg/kg bw/day were negative, i.e., fecal excretion exceeded intake. Furthermore, the mean absorption for the 28 balance studies was approximately 5%.

Table 5. Comparison of lead concentrations in breast milk and maternal or cord blood

Pb milk (ppb)[a]	Pb blood (µg/l)	Pb milk/ Pb blood	*n*	Country	Reference
0.73 ± 0.70	29 ± 8 (mat)[b]	2.5	9	Australia	This study
0.73 ± 0.70	24 ± 8 (cord)	3.0	9	Australia	This study
0.7 ± 0.4	32 ± 8	2.2	75	Sweden	(*15*)
2.6 ± 1.6	39 ± 14 (mat)	6.7	27	Germany	(*25*)
2.6 ± 1.6	30 ± 16 (cord)	8.7	17	Germany	(*25*)
25	460 ± 20	5.4	35	Mexico	(*34*)
2.8 ± 1.6	119 ± 94 (mat)	2.4	39	United States	(*26*)
17 ± 2	72 ± 3 (cord)	23.6	100	United States	(*41*)
21	200	10.5	97	Scotland	(*42*)
48 ± 12	151 ± 14	31.5	114	Malaysia	(*30*)
48	114 ± 31	41.8	114	Malaysia	(*30*)
25.3 ± 11	173[c] urban	14.6	89	Malaysia	(*35*)
21.1 ± 10	158[c] rural	13.3	91	Malaysia	(*35*)
35.8 ± 15	37.0 ± 12.7	97	51	Austria	(*43*)
10	340	2.9	1	United States	(*44*)
10	290	3.4	1	United States	(*44*)
64 ± 4	213 ± 12	30.0	38	Hungary	(*45*)
209 ± 29	234 ± 35	89	26	Russia	(*46*)
1.04 mean (0.55 median)	NA		210	Canada	(*24*)
1.7	NA		72	Czechoslovakia	(*27*)
13.3 (urban)	NA		20	Germany	(*36*)
9.1 (rural)	NA		20	Germany	(*36*)
30	NA		39	United Kingdom	(*47*)
69.6 ± 17[d]	NA		25	United Arab Emirates	(*48*)
127 (urban)	NA		20	Italy	(*49*)
46 (rural)	NA		34	Italy	(*49*)
85 ± 33	NA		164	Thailand	(*37*)
2.9 ± 0.6[e]	NA		74	Guatemala	(*28*)
14.9 ± 0.9[e]	NA		68	Hungary	(*28*)
4.9 ± 1.2[e]	NA		14	Nigeria	(*28*)
16.6 ± 1.2[e]	NA		63	Philippines	(*28*)
16.8 ± 1.0[e]	NA		32	Sweden	(*28*)
5.0 ± 0.8[e]	NA		69	Zaire	(*28*)

Abbreviations: mat, maternal; NA, not available.
[a]Units for breast milk are standardized to parts per billion.
[b]Blood sample taken at closest time to parturition.
[c]General population figures.
[d]Over 94% used Kohl cosmetic.
[e]Analytical problems were alluded to in this joint study.

Breast Milk Lead Concentrations

Our lead concentrations in breast milk of 0.09–3.1 µg Pb/kg or ppb (mean 0.7) are among the lowest recorded (Table 5). Because of the importance of breast milk to infants, there have been many investigations of lead in breast milk, but most of these are often orders of magnitude higher than our values. As can be seen from Table 5, only those of the Swedish investigators have levels consistent with ours, although breast milk concentrations in subjects from Canada (*24*), Germany (*25*), the United States (*26*), and the former Czechoslovakia (*27*) are also less than 3 ppb. Lead concentrations in breast milk are very low and, like the collection and analysis for plasma or serum leads, unless extreme precautions are taken, contamination is a major concern. It is not surprising that very few studies of lead in plasma or serum are undertaken because investigators have recognized, belatedly, the difficulties in these analyses. Many investigators, however, appear to express few concerns over the analyses of breast milk. This is even more surprising because the complications in the analyses of breast milk are even greater than for serum, given the large amount of fatty material in the sample. To overcome the fat problem, investigators have commonly resorted to dry ashing samples in a muffle furnace, where it is almost impossible to control contamination. Furthermore, dry ashing can result in loss through volatilization so that breast milk data obtained by dry ashing could be both artifactually low and high.

Recognition of analytical problems in analyses of breast milk was alluded to in the World Health Organization/International Atomic Energy Agency (WHO/IAEA) joint

study of breast milk from Guatemala, Hungary, Nigeria, Philippines, Sweden, and Zaire (*28*). These problems were indicated by the wide range in lead concentrations for the quality control standard HM-1, which gave a median ± SD of 0.09 ± 32 mg Pb/g, dry. Further indications of analytical difficulties were shown by, for example, the breast milk data for Sweden. The median ± SD for 32 samples was 16.8 ± 1.0 µg Pb/l, whereas a slightly later study by Hallén et al. (*15*) gave values of 0.7 ± 0.7 µg Pb/kg (Table 5). Because of these possible analytical difficulties, the WHO/IAEA results for lead in breast milk should be treated with caution until verified by follow-up investigations. The ease with which breast milk can be contaminated was reported by Hu et al. (*29*); in their study of lead in blood and bone of Boston mothers, Hu and co-workers suggested that the high levels of lead in breast milk, which they did not report, were contaminated from the foil around the alcohol wipes used to clean nipples.

One method that allows for some verification of the accuracy of the results is to compare the data for breast milk with maternal blood lead concentrations. The ratios expressed as a percentage of lead concentrations in breast milk to whole blood for data from 1980 onward are given in Table 5 and plotted in Figure 3. Small variations in the ratio can arise if cord or maternal blood lead levels are used, but these variations do not negate any conclusions that can be drawn from the data. It appears that any data that have a ratio of the concentration of lead in breast milk to the concentration of lead in maternal blood greater than 15% should be treated with caution. The problem more likely arises from the breast milk data because of the low concentrations of lead in the samples. Thus, it would seem that high lead concentrations in breast milk relative to blood leads are an indication of contamination during sampling and/or analysis. This would apply particularly to the Austrian study and probably also to the Malaysian studies shown in Table 5, in spite of implementation of quality control measures by Ong et al. (*30*). In the latter case, data for milk and blood from urban and rural communities from Malaysia seem very high.

The low percentage of less than 3% of lead in breast milk relative to whole blood is similar to the levels observed in serum or plasma; the high precision study of Manton and Cook (*31*) and Stauber et al. (*32*) showed that the serum lead/blood lead ratio ranged from 0.5 to 1.5%.

An alternative interpretation of the data shown in Figure 3 is that there are two trends: the one of shallow slope preferred here and another of higher slope incorporating the data from all the studies. The latter interpretation would imply either a linear or curvilinear relationship between lead in breast milk and maternal blood lead for high blood lead concentrations, as is the case of plasma versus blood lead concentration, shown by Manton and Cook (*31*) and De Silva (*33*). The interpretation of a curvilinear relationship between lead in breast milk and maternal blood lead is not considered valid because the data for Mexico City include some of the highest blood lead concentrations measured in recent times, and Namihara et al. (*34*) already established that there was a significant linear relationship between lead in breast milk and maternal blood lead concentration for their cohort (see below).

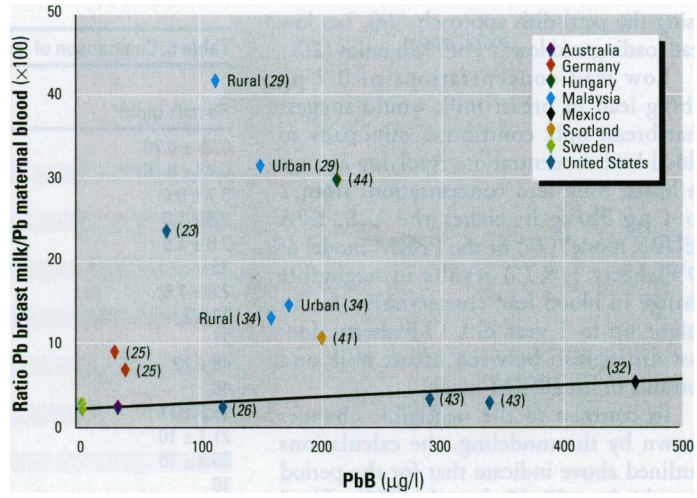

Figure 3. Lead concentrations in maternal blood versus the concentration of lead in breast milk/concentration in maternal whole blood (×100) from several studies over the past 15 years. The numbers in parentheses are the reference numbers. Data for the Austrian (*43*) and Russian (*46*) studies are excluded. The line of best fit is drawn through data from Australia, Sweden, Mexico, and some from the United States that are considered to represent the realistic relationships between lead in maternal blood and breast milk. Australia represents this study.

The data for subject 1042 have been treated as an outlier because this subject had a blood lead concentration on arrival in Australia of 20 µg/dl. The ratio percent of breast milk lead/blood lead is about 0.4% and could fit the curvilinear relationship hypothesis or indicate that the blood lead concentration of 20 µg/dl is a nonsteady-state measurement, i.e., was an abrupt spike of exposure.

There were no systematic variations in breast milk lead concentration for subjects for whom it was possible to serially sample, although in three of the subjects there was an increase at or after about 90 days. This increase could not be related to any changes in diet such as beginning of infant formula, general health, or development of the infants. There are very few investigations of serial sampling of breast milk, let alone longitudinal investigations of individuals, and only one that continued for 3 months or longer postpartum. Ong et al. (*30*) collected samples from each of 114 infants at 3, 7, 10, 14, and 20 days and at 1 month postpartum, but did not observe significant changes over the month. Likewise, Huat et al. (*35*) did not observe any specific patterns over periods ranging up to 12 months, but this was based on cross-sectional data. Sternowsky and Wessolowski (*36*) carried out the most systematic investigation with breast milk from two groups of 10 subjects from days 2, 5, and 15 and then every 2 weeks up until 90 days postpartum. In the rural group, they observed a tendency of decreasing lead concentrations toward the end of lactation, whereas there was a tendency of increasing levels in the urban mothers. The differences were significant only on day 45. In a cross-sectional study, Chatranon et al. (*37*) subdivided their breast milk data into 11 groups including 2, 3–5, 6–8, and 9+ months. The lead concentrations were very high (85 ± 33 ppb) and they found no specific pattern. Thus, at this stage, there are no unequivocal trends for lead concentrations in breast milk over time, but longitudinal high quality data are lacking, apart from the present study.

Relationships of lead in whole blood and breast milk for animals appear quite different from those for humans. For example, Tachon et al. (*38*) measured a 1/1 ratio of lead in breast milk/blood in a group of control monkeys, with a mean blood lead level of 51 µg/l, and a ratio of about 2/1 for a group dosed with lead, with a mean blood lead level of 1,161 µg/l. At blood lead concentrations above 30 µg/l, Hallén et al. (*39*) observed breast milk/blood lead ratios in mice to be greater than 1. Hallén (*14*) suggested that the binding of lead to casein in milk may explain the differences in milk excretion of lead between different species. For example, rats and mice have high concentrations of casein in milk (60–90 mg/ml milk) and show a substantial transfer of lead into milk (lead in milk/lead in plasma >100-fold), whereas human milk has very low casein concentrations (2–6 mg/ml milk) and the lowest reported excretion of lead into

milk. A high casein concentration may explain the unusually high ratio of 10/1 of milk lead/blood lead of rat dams fed lead acetate (*40*).

Relationships of Breast Milk to Other Indices

Infants. In spite of the limited number of measurements and the low concentrations of lead in breast milk compared with infant whole blood, the significant statistical relationship for the $^{207}Pb/^{206}Pb$ ratio and lead concentration between breast milk and blood over the 60–90 day period (Table 3) is consistent with the mixing calculations. These calculations indicate that from 36 to 80% of lead in blood in the first 60–90 days postpartum is contributed from breast milk (Table 4).

The lack of a significant statistical relationship between breast milk and infant urine at 60 days is consistent with our earlier conclusions that the higher $^{206}Pb/^{204}Pb$ ratios in urine compared with blood and breast milk in five of eight migrant infants arose from mobilization of infant skeletal lead (*23*).

The lack of statistical significance for the isotopic ratios in formula/food and infant blood (Table 3) may arise from the large isotopic variations between brands of some infant formula, along with mixed breast milk/formula feeding and the difficulty of adjusting for these complexities in the statistical models. Isotopic variations between brands may also account for the relationships between formula (only) or formula/food and infant urine (Table 3), with lead concentration in the formula being the main predictor of variables in the infant urine. This was also the case for formula and infant blood relationships.

Mothers. The statistical analyses for mother's blood versus breast milk, with milk as the outcome, did not yield any useable results. There was, however, a statistically significant relationship between the lead concentration data for cord blood and first breast milk sample collected at about 30 days (Table 3, Table 6). The data for subject 1042 were omitted from this regression because she had a blood lead of 20 µg/dl on arrival in Australia, considerably higher than for any of the others subjects discussed here. Several authors have reported a significant correlation between lead in the maternal blood and breast milk, and these results are summarized in Table 6. Also listed in Table 6 are a number of studies in which no correlation or a poor correlation was observed. One explanation for the different relationships noted in Table 6 may lie in the time of sampling, but given the variation in Table 6, sampling time can only be part of the explanation. For example, Hallén et al. (*15*) did not detect a significant correlation between blood and breast milk at 6 weeks postpartum, but observed a small significant correlation between lead levels in blood at delivery and breast milk at 6 weeks postpartum (Table 6). Because there are increased levels of lead mobilized from the skeleton during the postpregnancy period compared with during pregnancy (*3*), this may be an added complication to any systematic relationships between blood and breast milk. Hallén et al. (*39*) observed a nonlinear relationship between lead in maternal blood and breast milk and lead in plasma and whole blood in mice that had been dosed with a ^{203}Pb radioactive tracer. A nonlinear relationship between lead in whole blood and plasma has been reported for humans (*31,33*).

Even for subjects from highly polluted areas such as Mexico City (*34*) with mean blood lead levels of 46 µg/dl (and ranging up to 99 µg/dl), the ratio of lead concentration in breast milk to lead concentration in maternal whole blood is not markedly different from those with low blood lead levels (Fig. 3, Table 5). Even though there are limited data, the conclusion from Figure 3 is for a linear relationship between lead in breast milk and whole blood, at least for the data defining the array of low slope.

The significant statistical relationship between mother's diet and breast milk should be expected because it has been shown that other toxins and drugs are readily transferred from mother to infant in breast milk (*1*). Furthermore, as the mothers' diet generally has a lower $^{206}Pb/^{204}Pb$ ratio than their skeletal lead, it might be expected that their breast milk would exhibit a decrease in $^{206}Pb/^{204}Pb$ over time, as observed in Figure 2.

Conclusions

The benefits of breast milk must be judged by a far more complex set of considerations than bioavailability of lead unless maternal exposures are very high, such as around smelters, house renovations with leaded paint, dietary sources from lead-glazed pottery, cosmetics, and traditional medicine. If the mother had long-term exposure in such environments, an additional source of lead would be from mobilization of skeletal stores during lactation. In these circumstances it would be worthwhile to measure lead concentrations in breast milk. However, for the analyses to be of any value, rigid sampling and analytical protocols must be followed to avoid specimen contamination. If not, the exercise is fruitless. On the other hand, if further well-conducted investigations verify the linear relationship between breast milk and blood described in this paper, blood lead analyses may suffice to provide indications of exposure of the infant to lead from breast milk. Likewise, further investigations of serial sampling for periods longer than those reported in the literature (90 days) should be undertaken to determine if the increases noted in three of our subjects after about day 70 are general. Once again, there may be cause for concern for subjects with a high lead exposure such as smelter or hazardous waste site communities. In this respect, the data for the Mexican smelter shows that the ratio percent of breast milk lead to blood lead is about 5.4% at the mean blood lead concentration of about 46 µg/dl. Hence, the use of a fixed ratio derived at low blood lead concentrations will underestimate breast milk lead and thereby infant lead intakes with breast-feeding. The converse is also important, that is, a ratio determined at high blood lead concentrations and lead exposure may be higher than in cases where blood lead concentrations are lower and the breast milk equivalent would be proportionately lower.

During the past decade, sources of environmental lead have decreased as a result of, for example, the phase out of lead in gasoline and banning of lead solder from food and beverage cans and water supplies.

Table 6. Comparison of regression analyses for lead concentrations in maternal whole blood or cord blood and breast milk

r^2	*p*-Value	*n*	Reference	Time of blood sampling
0.34[a]	<0.05	75	(*15*)	At delivery[b]
	NS[c]	75	(*15*)	6 weeks postpartum
0.88	<0.0001	35	(*34*)	Not given, but postpartum
0.29	<0.01	114	(*30*)	At delivery
0.55	<0.001	97	(*42*)	Not given, but postpartum
0.18	0.11 (NS)	100	(*41*)	Cord
	NS	39	(*27*)	>1 month postpartum
0.03	0.28 (NS)	40[d]	This study	Within 1 month prior to delivery
0.32	0.053	12[d]	This study	Cord vs. 1st breast milk (~30 days)

NS, not significant.

[a]Blood at delivery and breast milk at 6 weeks postpartum.

[b]Maternal blood at delivery.

[c]Blood and breast milk at 6 weeks postpartum.

[d]Data for subject 1042 omitted.

Review of available data on dietary exposure of infants to lead indicate a decline from about 10 µg/kg bw/day in the 1980s to less than 1 µg/kg bw/day observed in this study. These major changes in exposure require a reassessment of the earlier data on fractional absorption of lead by infants through new clinical investigations or biokinetic studies. As noted above, the fractional absorption on balance studies in which dietary intake was less than 5 µg/kg bw/day indicate values of about 5% (*5*), but confirmatory investigations were never undertaken. Various models of pharmacokinetics of lead are likely to be concentration dependent. Because these models are used to support economically far-reaching decisions on tolerable levels of lead in environmental media, it is critical that appropriate clinical data be available.

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